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By: [Signature]

Attorney Docket No. 14538A-004610US **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

David M. Hockenberry *et al.*

Application No.: 10/069,431

Filed: August 18, 2000

For: COMPOSITIONS AND METHODS
FOR MODULATING APOPTOSIS
IN CELLS OVER-EXPRESSING
Bcl-2 FAMILY MEMBER
PROTEINS

Examiner: Not assigned yet

Art Unit: Not assigned yet

**INFORMATION DISCLOSURE
STATEMENT**

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants direct the Examiner's attention to the references below, also listed on the accompanying Form PTO-1449. A copy of each is also enclosed.

The following U.S. Patents are set forth below by issue date:

- AA. U.S. Patent No. 5,641,866, issued on June 24, 1997 to Reed *et al.*
- AB. U.S. Patent No. 5,643,727, issued on July 1, 1997 to Reed *et al.*
- AC. U.S. Patent No. 5,659,024, issued on Aug. 19, 1997 to Reed *et al.*
- AD. U.S. Patent No. 5,686,595, issued on Nov. 11, 1997 to Reed *et al.*
- AE. U.S. Patent No. 5,702,897, issued on Dec. 30, 1997 to Reed *et al.*
- AF. U.S. Patent No. 5,734,033, issued on March 31, 1998 to Reed
- AG. U.S. Patent No. 5,744,310, issued on April 28, 1998 to Reed
- AH. U.S. Patent No. 5,994,564, issued on Nov. 30, 1999 to Van Sickle
- AI. U.S. Patent No. 5,998,583, issued on Dec. 7, 1999 to Korsmeyer

The following articles are set forth in alphabetical order:

- AJ. Bernardi *et al.*, "The permeability transition pore. Control points of a cyclosporine A-sensitive mitochondrial channel involved in cell death," *Biochim. Biophys. Acta* 1275:5-9 (1996)
- AK. Charlotte *et al.*, "Immunohistochemical detection of *bcl-2* protein in normal and pathological human liver," *Am. J. Pathol.* 144:460-65 (1994)
- AL. Cheng *et al.*, "Conversion of Bcl-2 to a Bax-like death effector by caspases," *Science* 278:1966-68 (1997)
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- AQ. Decaudin *et al.*, "Bcl-2 and Bcl-X_L antagonize the mitochondrial dysfunction preceding nuclear apoptosis induced by chemotherapeutic agents," *Cancer Res.* 57:62-67 (1997)
- AR. Fisher, "Apoptosis in cancer therapy: crossing the threshold," *Cell* 78:539-42 (1994)
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- AT. Hu *et al.*, "Bcl-X_L interacts with Apaf-1 and inhibits Apaf-1-dependent caspase-9 activation," *Proc. Natl. Acad. Sci. USA* 95:4386-91 (1998)
- AU. Hueber *et al.*, "Thy-1 triggers mouse thymocyte apoptosis through a *bcl-2*-resistant mechanism," *J. Exp. Med.* 179:785-96 (1994)
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- AW. Kelekar *et al.*, "Bcl-2-family proteins: the role of the BH3 domain in apoptosis," *Trends Cell Biol.* 8:324-30 (1998)

- AX. Kluck *et al.*, "The release of cytochrome c from mitochondria: a primary site for Bcl-2 regulation of apoptosis," *Science* 275:1132-36 (1997)
- AY. Kroemer *et al.*, "Mitochondrial control of apoptosis," *Immunol. Today* 18:44-51 (1997)
- AZ. Kroemer, "The proto-oncogene Bcl-2 and its role in regulating apoptosis," *Nature Med.* 3:614-20 (1997)
- BA. Liu *et al.*, "Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c," *Cell* 86:147-57 (1996)
- BB. Memon *et al.*, "Bcl-2 blocks glucocorticoid- but not Fas- or activation-induced apoptosis in a T cell hybridoma," *J. Immunol.* 155:4644-52 (1995)
- BC. Minn *et al.*, "Expression of Bcl-x_L can confer a multidrug resistance phenotype," *Blood* 86:1903-10 (1995)
- BD. Miyoshi *et al.*, "A model of antimycin A binding based on structure-activity studies of synthetic antimycin A analogues," *Biochim. Biophys. Acta* 1229:149-54 (1995)
- BE. Muchmore *et al.*, "X-ray and NMR structure of human Bcl-X_L, an inhibitor of programmed cell death," *Nature* 381:335-41 (1996)
- BF. Newmeyer *et al.*, "Cell-free apoptosis in *Xenopus* egg extracts: inhibition by Bcl-2 and requirement for an organelle fraction enriched in mitochondria," *Cell* 79:353-64 (1994)
- BG. Pan *et al.*, "Caspase-9, Bcl-X_L, and Apaf-1 form a ternary complex," *J Biol. Chem.* 273:5841-5 (1998)
- BH. Petit *et al.*, "Mitochondria and programmed cell death: back to the future," *FEBS Letters* 396:7-13 (1996)
- BI. Rieske, "Inhibitors of respiration at energy-coupling site 2 of the respiratory chain," *Pharm Ther.* 11:415-50 (1980)
- BJ. Sattler *et al.*, "Structure of Bcl-x_L-Bak peptide complex: recognition between regulators of apoptosis," *Science* 275:983-86 (1997)
- BK. Shimano *et al.*, "Total synthesis of the antifungal dilactones UK-2A and UK-3A: the determination of their relative and absolute configurations, analog synthesis and antifungal activities," *Tetrahedron* 54:12745-74 (1998)

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BM. Susin *et al.*, "The central executioner of apoptosis: multiple connections between protease activation and mitochondria in Fas/APO-1/CD95- and ceramide-induced apoptosis," *J. Exp. Med.* 186:25-37 (1997)

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BO. Tokutake *et al.*, "Structural factors of antimycin A molecule required for inhibitor action," *Biochim. Biophys. Acta* 1185:271-78 (1994)

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BQ. van Tamelen *et al.*, "The chemistry of antimycin A. X. Structure of the Antimycins," *J. Am. Chem. Soc.* 83:1639-1646 (1961)

BR. Wu *et al.*, "Establishment and characterization of differentiated, nontransformed hepatocyte cell lines derived from mice transgenic for transforming growth factor α ," *Proc. Natl. Acad. Sci. USA* 91:674-78 (1994)

BS. Wu *et al.*, "Autonomous growth in serum-free medium and production of hepatocellular carcinomas by differentiated hepatocyte lines that overexpress transforming growth factor α ," *Cancer Res.* 54:5964-73 (1994)

BT. Xia *et al.*, "Electrical stimulation of neonatal cardiomyocytes results in the sequential activation of nuclear genes governing mitochondrial proliferation and differentiation," *Proc. Natl. Acad. Sci. USA* 94:11399-404 (1997)

BU. Zamzami *et al.*, "Sequential reduction of mitochondrial transmembrane potential and generation of reactive oxygen species in early programmed cell death," *J. Exp. Med.* 182:367-77 (1995)

BV. Zamzami *et al.*, "Inhibitors of permeability transition interfere with the disruption of the mitochondrial transmembrane potential during apoptosis," *FEBS Letters* 384:53-57 (1996)

BW. Zamzami *et al.*, "Mitochondrial control of nuclear apoptosis," *J. Exp. Med.* 183:1533-44 (1996)

BX. Zoratti *et al.*, "The mitochondrial permeability transition," *Biochim. Biophys. Acta* 1241:139-76 (1995)

It is respectfully requested that the cited information be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

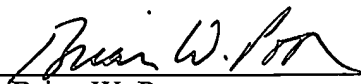
Applicants believe that their invention as claimed is patentable over the above references taken alone or in any combination. However, Applicants reserve the right to demonstrate that their claimed invention was made prior to any one or more of the above-identified references. No inference should be drawn as to the pertinence of the references based on the order in which they are presented.

Applicant respectfully requests that the Examiner review the foregoing references to make his own determination of the patentability of the present invention and that the references be made of record in the file of this application.

Applicant believes that no fee is required for submission of this statement, since it is being submitted prior to the first Office Action. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,

Dated: 18 March 2003

By: 
Brian W. Poor
Reg. No. 32,928

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Fax: (415) 576-0300



FORM PTO-1449 (Modified) LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Attorney Docket No.: 14538A-004610US	Application No.: 10/069,431
	Applicant: David M. Hockenberry <i>et al.</i>	
	Filing Date: Aug. 18, 2000	Group: Unassigned

Reference Designation	U.S. PATENT DOCUMENTS	Page 1 of 1
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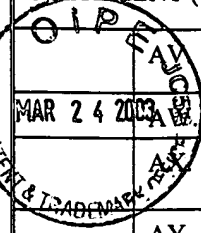
Examiner Initial		Document No.	Date	Name	Class	Sub-class	Filing Date (If Appropriate)
	AA.	US 5,641,866	06-24-97	Reed <i>et al.</i>			
	AB.	US 5,643,727	07-01-97	Reed <i>et al.</i>			
	AC.	US 5,659,024	08-19-97	Reed <i>et al.</i>			
	AD.	US 5,686,595	11-11-97	Reed <i>et al.</i>			
	AE.	US 5,702,897	12-30-97	Reed <i>et al.</i>			
	AF.	US 5,734,033	03-31-98	Reed			
	AG.	US 5,744,310	04-28-98	Reed			
	AH.	US 5,994,564	11-30-99	Van Sickle			
	AI.	US 5,998,583	12-07-99	Korsmeyer			

FOREIGN PATENT DOCUMENTS							
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		Document No.	Date	Country	Class	Sub-class	Translation (Yes/No)

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)							
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	AJ.	Bernardi <i>et al.</i> , "The permeability transition pore. Control points of a cyclosporine A-sensitive mitochondrial channel involved in cell death," <i>Biochim. Biophys. Acta</i> 1275:5-9 (1996)					
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	AL.	Cheng <i>et al.</i> , "Conversion of Bcl-2 to a Bax-like death effector by caspases," <i>Science</i> 278:1966-68 (1997)					
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	AN.	Clem <i>et al.</i> , "Modulation of cell death by Bcl-X _L through caspase interaction," <i>Proc. Natl. Acad. Sci. USA</i> 95:554-59 (1998)					
	AO.	Cosulich <i>et al.</i> , "Regulation of apoptosis by BH3 domains in a cell-free system," <i>Curr Biol.</i> 7:913-20 (1997)					
	AP.	Cosulich <i>et al.</i> , "Bcl-2 regulates amplification of caspase activation by cytochrome c," <i>Curr Biol.</i> 9:147-50 (1999)					
	AQ.	Decaudin <i>et al.</i> , "Bcl-2 and Bcl-X _L antagonize the mitochondrial dysfunction preceding nuclear apoptosis induced by chemotherapeutic agents," <i>Cancer Res.</i> 57:62-67 (1997)					
	AR.	Fisher <i>et al.</i> , "Apoptosis in cancer therapy: crossing the threshold," <i>Cell</i> 78:539-42 (1994)					
	AS.	Holinger <i>et al.</i> , "Bak BH3 peptides antagonize Bcl-X _L function and induce apoptosis through cytochrome c-independent activation of caspases," <i>J Biol. Chem.</i> 274:13298-304 (1999)					
	AT.	Hu <i>et al.</i> , "Bcl-X _L interacts with Apaf-1 and inhibits Apaf-1-dependent caspase-9 activation," <i>Proc. Natl. Acad. Sci. USA</i> 95:4386-91 (1998)					
	AU.	Hueber <i>et al.</i> , "Thy-1 triggers mouse thymocyte apoptosis through a <i>bcl-2</i> -resistant mechanism," <i>J. Exp. Med.</i> 179:785-96 (1994)					

FORM PTO-1449 (Modified)		Attorney Docket No.: 14538A-0046	Application No.: 10/069,431
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)		Applicant: David M. Hockenberry <i>et al.</i>	
		Filing Date: Aug. 18, 2000	Group: Unassigned
		Hunter <i>et al.</i> , "A peptide sequence from Bax that converts Bcl-2 into an activator of apoptosis," <i>J. Biol. Chem.</i> 271:8521-24 (1996)	
		Kelekar <i>et al.</i> , "Bcl-2-family proteins: the role of the BH3 domain in apoptosis," <i>Trends Cell Biol.</i> 8:324-30 (1998)	
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	AY.	Kroemer <i>et al.</i> , "Mitochondrial control of apoptosis," <i>Immunol. Today</i> 18:44-51 (1997)	
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	BH.	Petit <i>et al.</i> , "Mitochondria and programmed cell death: back to the future," <i>FEBS Letters</i> 396:7-13 (1996)	
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FORM PTO-1449 (Modified)

Attorney Docket No.: 14538A-00461

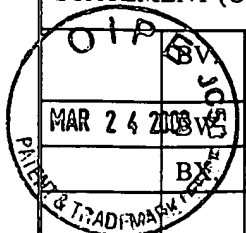
Application No.: 10/069,431

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Applicant: David M. Hockenberry *et al.*

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Zamzami *et al.*, "Mitochondrial control of nuclear apoptosis," *J. Exp. Med.* 183:1533-44 (1996)

Zoratti *et al.*, "The mitochondrial permeability transition," *Biochim. Biophys. Acta* 1241:139-76 (1995)

EXAMINER

DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.